STUDY TO EVALUATE THE EFFECT OF DEXMEDETOMIDINE IN ATTENUATING THE HEMODYNAMIC AND NEUROENDOCRINAL RESPONSES TO SKULL-PIN HEAD-HOLDER APPLICATION DURING CRANIOTOMY

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IN

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MADRAS MEDICAL COLLEGE

CHENNAI – 600 003.

CERTIFICATE

This is to certify that the dissertation entitled, **"STUDY TO EVALUATE THE EFFECT OF DEXMEDETOMIDINE IN ATTENUATING THE HEMODYNAMIC AND NEUROENDOCRINAL RESPONSES TO SKULL-PIN HEAD-HOLDER APPLICATION DURING CRANIOTOMY"** submitted by **Dr. T. RENGANATHAN** in partial fulfillment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamil Nadu Dr. M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE, Madras Medical College, during the academic year 2009-2012.

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DECLARATION

I hereby declare that the dissertation entitled **"STUDY TO EVALUATE THE EFFECT OF DEXMEDETOMIDINE IN ATTENUATING THE HEMODYNAMIC AND NEUROENDOCRINAL RESPONSES TO SKULL-PIN HEAD-HOLDER APPLICATION DURING CRANIOTOMY"** has been prepared by me under the Guidance of **PROF. DR C.R.KANYAKUMARI M.D.,D.A.,** Professor and Director,Institute Of Anesthesiology And Critical Care, Madras Medical College, Chennai in partial fulfillment of the regulations for the award of the degree of M.D [Anaesthesiology], examination to be held inApril 2012. This study was conducted at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.I have not submitted this dissertation previously to any university for the award of any degree or diploma.

Place: Chennai **Dr. T. RENGANATHAN**

Date :

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CONTENTS

INTRODUCTION

The Mayfield skull-pin head holder is used to stabilize the head during neuro surgical procedures.

They support the head without any direct pressure on the face, allow access to the airway and hold the head firmly in one position that can be finely adjusted for optimal neurosurgical exposure.

Although it is an instrument of barbaric appearance, it is essential for operations in the sitting position and highly desirable for cervical or intracranial procedures in the prone or lateral position.

Different anesthetic and pharmacologic technique, including local anesthetic, narcotics, antihypertensive, and deepening of anesthesia with inhalation anesthetics, have been used to blunt this deleterious effect with variable success.

When properly applied, the pins cause considerable periosteal stimulation. This results in abrupt increase in BP and CBF under GA[1,2] .

These hemodynamic responses may lead to brain edema, increase in ICP or ICH in aneurysm patients. Different anesthetic techniques have been used to blunt this deleterious effect with variable success.[4-7]

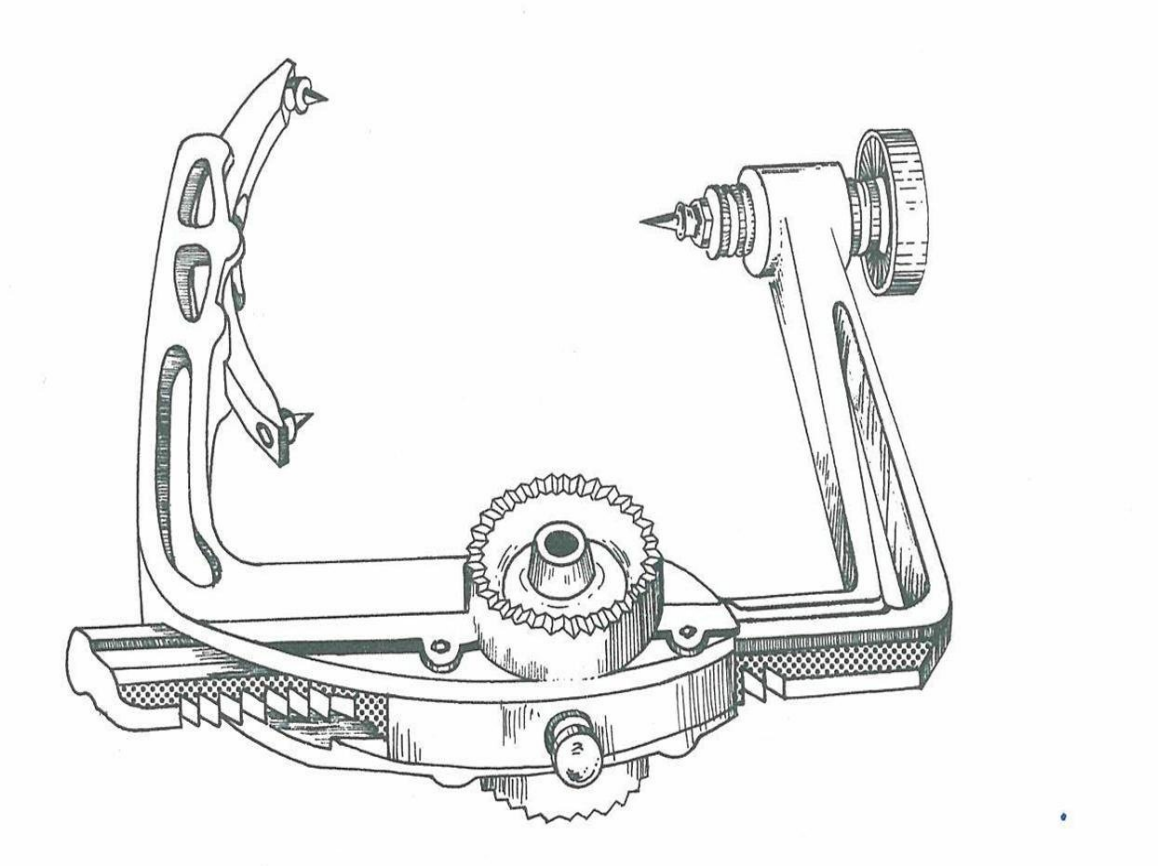
The stress response to intense nociceptive surgical stimulus is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system.

Attenuation of the cardiovascular and neuroendocrine responses to intense noxious stimuli during operation may improve outcome by beneficial effects on organ function.

Dexmedetomidine is a highly specific potent and selective α-2 adrenoreceptor agonist. It has sedative, analgesic, and anesthetic – sparing effects and it decreases HR, MAP and sympathetic nervous system activity in a dose dependent fashion[11,12]. Also it has the potential to exert inhibitory effects on cortisol and catecholamine synthesis13,14.

In this prospective randomized controlled study the hypotheses that dexmedetomidine would attenuate the increase in HR,MAP, plasma glucose, cortisol and prolactin concentrations to skull pin placement for craniotomies was investigated .

MAY FIELD HEAD REST



AIM OF THE STUDY

This study was done with the following intention : "*To evaluate the effect of dexmedetomidine in attenuating the hemodynamic and neuroendocrinal responses to skull pin head holder application during craniotomy*"

NOXIOUS STIMULUS – ITS RESPONSES

Prys-Roberts defined noxious stimulation as a mechanical, chemical, thermal, or radiation induced trespass causing potential or actual cell damage (fig. 1) shows the somatic and autonomic responses to noxious stimulation.

Noxious stimulation arises from somatic or visceral tissue and responses can be somatic or autonomic.

Somatic responses include both sensory and motor activity

Sensory response is perception of pain

A motor response is withdrawal of the stimulated part. This is the same concept that Eger and colleagues used more than four decades earlier when they defined the MAC as the drug concentration that blocked movement in response to noxious stimulation.

Prys – Roberts divided autonomic responses into four categories: *breathing, haemodynamic, sudomotor and hormonal*

HEMODYNAMIC RESPONSES

The hemodynamic response consists of autonomic responses to noxious stimuli, namely- increased sympathetic tone, which elevates blood pressure and the heart rate.

The sudomotor response consist of sweating, whereas the hormonal responses consist of catecholamine's and corticosteroids

Prys-Roberts considered pain relief, muscle relaxation and suppression of autonomic activity to be discrete pharmacologic effects. Some drugs can produce all these end points. Others produce only one or two.

STRESS RESPONSES

The stress responses was initially described by Hans selye as "the non- specific response of the body to any demand upon it"

The human body is an adaptable organism that has many interrelated mechanisms designed to identify, respond and neutralize both internal and external events that threatens or upsets homeostasis.

Anaesthesia and surgery involve manipulation of body physiology leading to activation of the body's responses to stress.

The stress response evolved as a mechanism for assisting the organism in reacting to immediate danger

Although once regarded positively as the body's defense mechanism. Today the stress response is regarded more equivocally since its physiologic consequences, especially increasing the output of various organ systems, may lead to increased morbidity and mortality by overtaxing already compromised organ system.

THE HYPOTHALAMIC PITUITARY AXIS:

The response to surgical and traumatic stress is triggered by hypothalamic activation secondary to afferent neuronal input from an area of injury such as inflammatory cytokines, TNF –α, IL-1 and IL6

Hypothalamic activation increases the activity of the sympathetic nervous system, which increases the output of the cardiovascular system, stimulates the adrenal medulla to secrete epinephrine and the pancreas to secrete glucagon

The endocrine system

The hypothalamic pituitary axis is the main controller of the endocrine system which in turn controls much of the body's metabolic functioning.

The endocrine hormones are major mediators of the metabolic response to stress. The hormones glucagon, cortisol and catecholamine oppose the effects of insulin on glucose and lipid metabolism and are thus called the counter regulatory hormones.

SYMPATHO ADRENERGIC SYSTEM

The sympathoadrenergic system composed of the sympathetic nervous system and adrenal gland, produces and secretes the catecholamines: norepinephrine epinephrine and dopamine.

Catecholamines have major effect on the cardiovascular system and also have major metabolic effect.

Glucagon- Insulin

Glucagon and insulin are both secreted by the pancreas, the former by the alpha cell, the later by the beta cells. The principal action of glucagon is to stimulate hepatic glycogenolysis and gluconeogenesis.

Serum glucagon concentration rises after most types of major surgery. The glucagon - insulin ratio increase because, insulin concentration decrease during surgery.

Glucocorticoid

Cortisol is a major stress hormone whose plasma levels are markedly elevated after surgical and traumatic stress. This is mainly due to enhanced secretion by the adrenal cortex.

In addition, this cortisol production is minimally suppressed by exogenous glucocorticoid administration. This was demonstrated by the inability of 24 mg/day of dexamethasone administered for 2days after craniotomy to suppress the elevated concentration of either ACTH or cortisol.

Cortisol is thought to cause insulin resistance by decreasing the rate of insulin activation of the glucose uptake system.

Cortisol is a vital mediator of stress because it facilitates catecholamine action and secretion, thus helping to maintain cardiovascular stability during surgical stress.

The counter regulatory hormones

The hormones, glucagon, catecholamine, and cortisol are called counter regulator hormones because they oppose the effect of insulin and act synergistically to increase glucose production.

PROLACTIN

Prolactin release from the pituitary gland is a very sensitive marker of both physical and physiological stress in mammals.

The prolactin surge results from a general increase in the adrenergic activity in the hypothalamus. The stress induced prolactin release is a rapid, strong and transient response that can be evoked by large number of medical and surgical procedures[26-28].

METHODS TO ATTENUATE HEMODYNAMIC AND STRESS RESPONSES

Control of hemodynamic parameters during neurosurgical procedure is of great concern to the neuro-anaesthesiologist whose goals include optimal cerebral perfusion pressure.

Also, the balance of myocardial oxygen supply and demand must be preserved to minimize the risk of per-operative myocardial ischemia and infarction.

Factors affecting myocardial oxygen supply and demand

Supply

1. Heart rate –diastolic time depends upon heart rate. Hence slower the heart rate, more the diastolic time and more the oxygen supply to the myocardium.
2. Coronary perfusion pressure – depends on aortic diastolic pressure and left ventricular end-diastolic pressure. It increases with a high aortic diastolic pressure and a low end diastolic pressure.
3. Arterial oxygen content – depends upon arterial oxygen tension and hemoglobin concentration.
4. Coronary vessel diameter.

Demand:

1. Basal requirement
2. Heart rate
3. Wall tension – preload, afterload
4. Contractility

A number of methods were used to attenuate cardiovascular response due to laryngoscopy and endotracheal intubation and skull pin placement

1. Deepening of general anesthesia

Inhalational agents – the deep level of anesthesia achieved by inhalational agents resulted in profound cardiovascular depression prior to skull pin placement

2. Lignocaine

Lignocaine has been demonstrated to produce intense analgesia when injected IV . Yukioka, et al demonstrated that the cough reflex was suppressed during intubation of trachea when plasma concentration of lignocaine was more than 2mcg/ml.

Levin R, et al demonstrated local mepivacaine infiltration safely protected against potentially dangerous increase in arterial pressure when the May field head holder was used

Mechanism

1. By increasing the depth of anesthesia
2. Potentiation of effect of N2O anesthesia and reduction of MAC of volatile agents
3. Direct cardiac depression
4. Peripheral vasodilatation
5. Anti-arrythmic properties

3. Clonidine

It is an alpha 2 receptor agonist. Clonidine 4 to 5 mcg/kg orally 60 to 120 minutes prior to intubation or 1 to 3 mcg/kg intravenously immediate prior to intubation attenuates hemodynamic responses. Mechanism of action of alpha 2 agonist is decreasing central sympathetic out flow, increasing the parasympathetic tone and by decreasing circulating nor-adrenaline concentration.

4. Intravenous vasodilators

Hydralazine

Sodium nitroprusside

Nitroglycerin

5. Narcotics

Fentanyl	Morphine
Alfentanyl	Pethidine
Sufentanyl	Nalbhuphine

Fentanyl is the most commonly used narcotic agent. It is a potent analgesic, has a short duration of action, does not increase intracranial tension and has minimal circulatory changes.

6. Adrenergic blocker

Long acting: metoprolol, phentolamine, propranolol, labetalol, Short acting: esmolol

Of these, esmolol is the most commonly used agent because of its ultra short action.

It reduces heart rate, systolic blood pressure, ejection fraction and cardiac index but it maintains coronary perfusion pressure.

7. Calcium channel blockers

Nifedipine, nicardipine , verapamil, diltiazem Of these agents, nicardipine has got superior action.

8. Sedative and anxiolytics:

Midazolam and magnesium sulphate.

PHARMOCOLOGY OF THE STUDY DRUG

Dexmedetomidine

It is a highly selective α2 – adrenergic agonist that produces sedation, hypnosis and analgesia.

History

The initiation for the use of α2 agonist in anesthesia resulted from observations made in patients during anesthesia who were receiving clonidine therapy. Dexmedetomidine was introduced in clinical practice in the United States in 1999. It was approved by FDA only as a short term (<24 hours) sedative for mechanically ventilated adult ICU patients.

Dexmedetomidine is now being used off-label outside of the ICU in various settings

Pharmacological profile

It is a highly selective α2 –adrenergic agonist. It shows a high ratio of specificity for the α2 receptor (α2/ α1 1600:1) compared with clonidine (α2/ α1 200:1), making it a complete α2 agonist. Dexmedetomidine belongs to the imidazole subclass of α2 receptor agonists, similar to clonidine. It is freely soluble in water.

Metabolism and pharmacokinetics

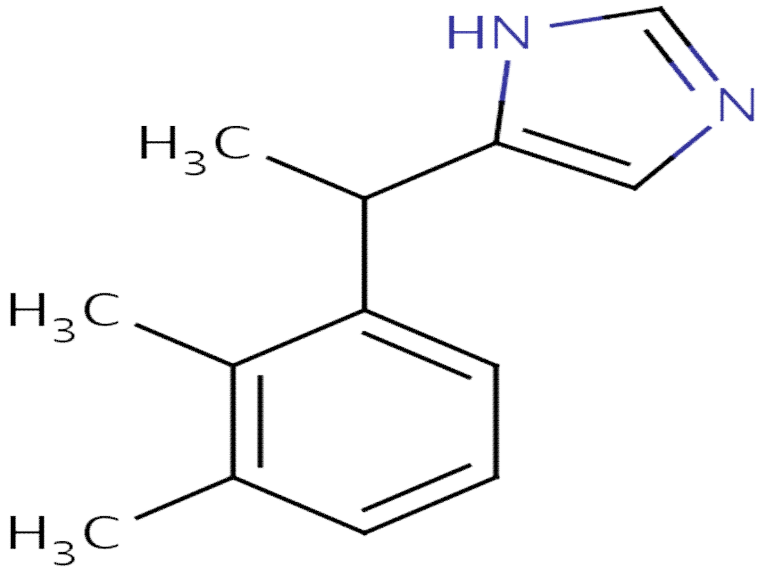
Dexmeditomidine has rapid redistribution half life -6min .Dexmedetomoidine is 94 % protein bound, and its concentration ratio between whole blood and plasma is 0.66. Metabolism: biotransformation by conjugation methylation (21%), or hydroxylation followed by conjugation in liver. The inactive metabolites are excreted in urine and feces. The elimination half-life of dexmedetomidine is 2-3 hours, with a context- sensitive half time ranging from 4 minutes after a 10 minute infusion to 250 minutes after an 8 hour infusion. No accumulation after infusions of 12-24 hrs duration.

Pharmacokinetics is similar in young adults and elderly.

Mechanism of actions

A selective α2-adrenoceptor agonist. Its action is unique and different. Three subtype of α2 adrenoreceptors have been described in humans: α2A, α2B and α2C

Structural formula



α2A adrenoreceptors are primarily distributed in the periphery, whereas α2B and α2C are in the brain and spinal cord.

- Presynaptic activation of α2- adrenoreceptors inhibit the release of nor -epinephrine.
- Postsynaptic activation of α2- adrenoreceptors in the central nervous system inhibits sympathetic activity and can decrease blood pressure and heart rate, so sedation and anxiolysis can result from this activity.
- Analgesia is provided through binding of dexmedetomidine to α2 adrenoreceptors in the spinal cord.

The overall response to α2adrenoreceptor agonist is related to the stimulation of α2adrenoreceptor located in the central nervous system and spinal cord. The α2 agonists produce their sedative – hypnotic effect by an action on α2 receptor in the locus caeruleus and an analgesic action at α2 receptors within the locus caeruleus and within the spinal cord.

Action

Effect on central nervous system

Sedation

The α2 agonists act through the endogenous sleep- promoting pathways to exert their sedative effect.

It produces a unique sedative quality **– someone be clinically sedated yet arousable**

- Patient sedated , remaining so when unstimulated . but when stimulated they are arousable, alert, and able to respond without becoming uncomfortable
- It's also observed that they would quickly return to their sleep –like state.

- This characteristic allows for “daily wake up” tests to be done in a safe fashion.

- Despite sound levels of sedation with dexmedetomidine, there is limited respiratory depression, providing wide safety margins.

Analgesia

The analgesic effects of dexmedetomidine are complex. α2 agonists do have an analgesic effect when injected via the intrathecal or epidural route. The primary site of analgesic action is thought to be the spinal cord.

Systemic use of dexmedetomidine shows narcotic sparing. In the postoperative ICU setting, narcotic requirements were reduced by 50% when patients were receiving dexmedetomidine.

In human pain studies, the results of systemically administered dexmedetomidine are inconsistent. Modest reductions in pain was observed.

In the clinical setting, when pain is likely to occur, if dexmedetomidine is to be used, the addition of a narcotic seems warranted.

Other central nervous system effects

Dexmedetomidine in animal models of incomplete cerebral ischemia and reperfusion reduces cerebral necrosis and improves neurologic outcome by reducing the intracerebral catecholamine outflow and the reduction of the excitatory neurotransmitter glutamate during injury.

Dexmedetomidine also is able to reduce muscle rigidity after high-dose opioid administration.

Effects on the respiratory system

Dexmedetomidine at concentrations producing significant sedation reduces minute ventilation, but retains the hypercapnic ventilatory response. The changes in ventilation appeared similar to those observed during natural sleep. Dexmedetomidine has been implicated in blocking histamine–induced bronchoconstriction in dogs.

Effects on cardiovascular system

The basic effects of α2 agonist on the cardiovascular system are decreased heart rate, decreased systemic vascular resistance and indirectly decreased myocardial contractility, cardiac output, and systemic blood pressure.

The hemodynamic effects of a bolus of dexmedetomidine in humans have show a biphasic response- an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline that occurred at 5 minutes after injection (probably due to the vasoconstrictive effects of dexmedetomidine when stimulating peripheral α2 receptors) followed by heart rate return to base line by 15 minutes, and blood pressure decrease 15% below base line by 1 hour.

The incidence of hypotension and bradycardia may be related to the administration of a loading dose. Omitting the loading dose or not giving more than 0.4μg/kg reduces the incidence of hypotension. Giving the loading dose over 20 minutes also minimizes the transient hypertension.

Dosage and administration

- Dexmedetomidine is supplied in a 2-ml ampoule, 100 mcg/ml.
- Dexmedetomidine must be diluted in 0.9% sodium chloride to achieve the required concentrations prior to administration. To prepare the infusion, withdraw 2ml of dexmedetomidine and add to 48 ml of 0.9% sodium chloride injection to total of 50 ml.
- The target concentration is 4mcg/ml. so 2ml of dexmedetomidine needs to be diluted to 50 ml in 0.9% sodium chloride.

- Loading dose – 0.5µg-1µg/kg (6-12ml)over 10min [36-72ml/hr]
- Maintenance -0.3µg-0.7µg /kg/hr(4-9ml/hr)
- Titration ±0.1µg/kg/hr- 1.25 ml/hr

Uses

Dexmedetomidine has been approved as a short term sedative for adult intubated patients in ICU. Given its well – documented beneficial effects of anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression , it also has been used in various other clinical scenarios .

1. Intensive care unit

Dexmedetomidine has following advantages for sedation in mechanically ventilated postoperative patients.

- Decreased requirement for opioids (>50%) when Dexmedetomidine is used for sedation compared with propofol or benzodiazepines.
- The PaO2/ FIO2 ratio was significantly higher in the Dexmedetomidine group
- Providing adequate sedation with minimal respiratory depression – can be used when weaning patients from the ventilator.

α 2 adrenoreceptor agonists have been used in the treatment of alcohol and drug withdrawal of narcotics, benzodiazepines, alcohol, and recreational drugs.

2. Anesthesia

a) Dexmedetomidine at IV doses of 0.33 to 0.67 µg/kg given 15 minutes before surgery attenuates the hemodynamic response to endotracheal intubation.

b) As a premedicant IM injection (2.5µg/kg)

c) Dexmedetomidine is used as a premedication 10 minutes before general surgery for cataract removal. Intra ocular pressure is decreased (33%) catecholamine secretion is reduced, perioperative analgesic requirements are less and recovery is very rapid

d) Dexmedetomidine is used for securing the airway with a fiberoptic intubation

e) Dexmedetomidine has been used for sedation for monitored anesthesia care in gynecological, urological, burns patients, trauma patients, and pediatric patients and in obese, OSA patients.

f) Sedation during regional anesthesia.

g) Dexmedetomidine is also useful as anesthetic adjuvant in Bariatric surgery, sleep-apnea patients, craniotomy aneurysm, AVM [hypothermia], cervical spine surgery, off pump CABG, vascular surgery, thoracic surgery, injury, burns, trauma, alcohol withdrawal.

Contraindications

- Infusion over 24 hours
- In obstetric procedures, caesarean section deliveries, the safety has not been studied.
- Patients with pre-existent severe bradycardia and related bradydysrhythmias (e.g., advanced heart block)
- Patients with impaired ventricular function (ejection fraction <30%)
- Patients who are hypovolemic or hypotensive.
- Patients with raised intracranial tension

Antidote

All effects of Dexmedetomidine could be antagonized easily by administering the alpha 2 – adrenoceptor antagonist *atipamezole* (A-17)

REVIEW OF LITERATURE

1. Tim G Costello et al had done a study comparing hemodynamic responses to intubation and pin head holder application in two groups of neuro surgical patients given oral clonidine (3mg/kg) or oral Temazepam (10-20mg) , 90 min before induction of anesthesia.

Mean arterial blood pressure (MAP) and heart rate were recorded before the induction of anesthesia and before and after intubation and application of the pin head holder. Interventions required to maintain hemodynamic stability were compared between groups. Pre induction sedation stores and MAP values were similar between groups. MAP was significantly lower ($p=0.031$) in the clonidine group after pin head holder application. The study was concluded by observing that clonidine was effective in reducing the MAP increase with pin head holder application in neurosurgical patients.

2. Menda F et al had conducted a study in which dexmedetomidine was compared with placebo or attenuate hemodynamic response to endotracheal intubation in patients undergoing fast track CABG.

50 patients who were receiving β- blocker treatment were given dexmedetomidine (1mcg/kg) or placebo before induction of anesthesia. Heart rate (HR) and blood pressure (BP) were monitored at baseline, after placebo on dexmedetomidine infusion, after induction of anesthesia and at one, three, and five minutes after endotracheal intubation.

In the dexmedetomidine group systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) were lower at all times in comparison to baseline values. In the placebo group SAP, DAP and MAP decreased after the induction of general anesthesia and five minutes after the intubation compared to baseline values. This decrease was not significantly different between the groups.

After the induction the drop in HR was higher in DEX group compared to PLA group. One minute after intubation, HR significantly increased in PLA group while, it decreased in the DEX group. The study was concluded by observing that dexmedetomidine can safely be used to attenuate the hemodynamic response to endotracheal intubation in patients undergoing myocardial revascularization receiving β- blockers.

3. Uyar, Yagmurdur et al had done a study in which dexmedetomidine was compared with a placebo to attenuate the

hemodynamic and neuro endocrinal responses to skull pin head holder application during craniotomy patients. In this study, 40 patients undergoing craniotomy with attachment of a pin holder were randomly assigned to one of two equal groups. The placebo group received saline, where as the treatment group (DEX group) received a single bolus of dexmedetomidine (1mcg/kg)., intravenously over 10 minutes before induction of anesthesia. Arterial blood pressure, heart rate and sequential concentrations of circulating cortisol, prolactin and blood glucose were measured. Relative to baseline and the other group, arterial blood pressure and heart rate decreased significantly after the administration of dexmedetomidine through skull pinning ($P<0.05$).

In both the groups plasma cortisol, prolactin and blood glucose increased significantly relative to baseline and after skull pin insertion. However the values were significantly increased in the placebo group compared with the DEX group. The results suggested that a single bolus dose of dexmedetomidine before induction of anesthesia attenuated the hemodynamic and neuroendocrinal responses to skull pin insertion in patients undergoing craniotomy.

4. Jellish W,et al conducted a study in which effects of clonidine premedication and scalp infiltration of lidocaine on hemodynamic responses to laryngoscopy and skull pin head holder insertion were

compared during skull base procedures . 34 patients undergoing skull base procedures were randomized to four groups. Group 1 received oral clonidine 5mcg/kg before surgery with 10-15 ml of 1% Lidocaine infiltrated at pin insertion sites. Group 2 received clonidine with saline infiltration. Group 3 received a placebo preoperatively and had lidocaine infiltrated at pin sites. Group 4 received a placebo and saline infiltration at pin insertion sites.

They concluded that clonidine attenuated HR increases after laryngoscopy, but not after H-H placement. Lidocaine injected at the pin sites reduced HR but MAP increased after H-H insertion. The combination of oral clonidine and scalp lidocaine blunted hemodynamic responses to both intubation and H-H placement

5. Scheinin et al conducted a study where IV dexmedetomidine was compared with a placebo to attenuate the sympathoadrenal responses to tracheal intubation

They studied in 24 ASA I patients, where either dexmedetomidine 0.6mcg/kg or saline was given I. V, 10 minutes before induction of anesthesia. They found that the required dose of thiopentone was significantly smaller ($p<0.001$) in the dexmedetomidine groups than in the

control group and the drug attenuated the cardiovascular responses to laryngoscopy and tracheal intubation.

They concluded that dexmedetomidine attenuated the sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and pre operative fentanyl .

The stress response to laryngoscopy and endotracheal intubation activates the sympathetic nervous system, which may increase the myocardial oxygen demand by increasing HR and arterial blood pressure.

Of the various methods, high dose opioids may completely inhibit the stress response . These high doses of opioids are impractical.

6. Mollick MT, et al in a study used low dose of lignocaine or low dose of opioids and observed the cardiovascular response after laryngoscopy and endotracheal intubation. They used 100 patients of both sexes. The cardiovascular parameters observed were HR,(SBP,) systolic blood pressure , diastolic blood pressure (DBP), and rate pressure product(RPP). Group 1 received lignocaine(1mg/kg) 2 minutes before induction of anesthesia.

Group II received inj. Pethidine 1mg/kg and inj. Lignocaine 1mg/kg intra venously . They concluded the study by observing that intravenous

lignocaine with pethidine did attenuate the sympathetic responses to laryngoscopy and endo tracheal intubation.

7. Dobblar DD, et al compared four techniques for preventing or blocking the hypertensive responses to the insertion of Mayfield headrest skull pin. Intravenous alfentanil, IV esmolol, IV thiopental sodium and local anesthesia using plain lidocaine.

Of the 40 patients undergoing intracranial surgery requiring the use of May field headrest skull pin, 20 min after anesthetic induction and 2-3 minutes prior to insertion of head rest skull pin, one of these three drugs was administered IV. (Alfentanil 10 mcg/kg , esmolol 1mg/kg or thiopental 1.5mg/kg). The fourth drug lignocaine was administered by injection into the scalp.

Blood pressure, heart rate were recorded immediately prior to and after pin insertion with balanced general anesthesia.

This study was concluded by observing that IV alfentanil and local injection of xylocaine in the scalp prevented the hemodynamic response to the insertion of skull pins. Neither esmolol nor thiopentone prevented the hypertensive response. They further concluded that the rapid onset and short half life of alfentanil , coupled with the absence of hemodynamic effects at the dose used is an alternative to the use of lidocaine injection.

8. Kenya ,et al conducted a study in which the efficacy of dexmedetomidine in attenuating the sympathoadrenal responses to tracheal intubation and also analyzed reduction in intra –operative anesthesia requirement.

Sixty patients scheduled for elective surgery of more than 3 hours were randomly selected .Control group received isoflurane-opioid and study group received isoflurane opioid- dexmedetomidine anesthesia given over 10 min before induction of anesthesia and continued in a dose of 0.2-0.7 mcg/kg/hr until skin closure. All patients were induced with thiopentone fentanyl and vecuronium. Hemodynamic variables were continuously recorded.

The study resulted in observing that in the dexmedetomidine group , the need for thiopentone and isoflurane was decreased by 30% and 32% respectively. The conclusion of the study was that perioperative infusion of dexmedetomidine is effective in attenuating sympathoadrenal responses to tracheal intubation. They also concluded that dexmedetomidine has significant anesthetic and opioid sparing effect.

9. Tanskanen PE, et al conducted a randomized double blind study in which dexmedetomidine was used as an adjuvant in patients undergoing intracranial tumor surgery. In that study, it was concluded that

there was an increased perioperative hemodynamic stability in patients undergoing brain tumor surgery without postoperative respiratory depression.

10. Bloor BC, et al conducted a study on the effects of intravenous dexmedetomidine in humans II Hemodynamic changes .

Here, they examined the hemodynamic effects of four selected IV doses in consenting healthy male volunteers. In a randomized trial subjects received 0(n=9), 0.25(n=6), 0.5(n=6), 1.0(n=6) or 2.0(n=10) mcg/kg of dexmedetomidine by infusion.

ECG, heart rate (HR), arterial blood pressure (MABP), bioimpedence cardiac output (CO) and plasma catecholamine concentration (CA) were monitored from 90 min before to 360 min after infusion. Plasma dexmedetomidine concentrations were measured.

The study was concluded thus: Even the lowest dose decrease CA (catecholamines) immediately to values close to 20PCG/ml for 5 hrs and 2min IV infusion of dexmedetomidine produced a transient increase in MABP and a longer lasting decrease in MABP and catecholamines .

MATERIALS AND METHODS

This study was conducted after obtaining approval from the institute ethical committee and patients' consent. Surgeon was informed of the study

Study design

Prospective randomized control study

Patient selection

Age group: 18 – 70 years

Forty consecutive ASA I and II patients aged between 18 years and 70 years old, undergoing elective craniotomy for resection of supratentorial tumor or clipping of an unruptured cerebral aneurysm with the aid of skull pin head holder were randomized in to 2 groups.

This study was done during the period from July 2011 to September 2011 in the department of anesthesia, GGH. Chennai 3

Exclusion criteria

1. History of endocrinology disease
2. HTN
3. IHD

4. 2° and 3°heart block
5. Pregnancy
6. Lactation
7. Symptoms and signs of raised ICP
8. Head injury
9. Presence of pre scalp incision
10. All tumor of hypophysis
11. Patients not willing to participate in the study.

Materials

1. Perfussor compact – syringe infusion pump.
2. Inj. Dexmedetomidine 2 ml amp, normal saline
3. Disposable 50 ml syringe
4. Extension tube
5. Weighing machine
6. Monitors- ECG ., NIBP , SPO2 , ETCO2

METHODOLOGY

Forty patients with the above criteria were divided in to two equal groups. Group DEX receives bolus dose of inj. Dexmedetomidine 1mcg/kg over ten minutes before induction of anesthesia.

Group NS receives equal amount of normal saline.

Pre operative investigations report like HB, blood urea , serum creatinine , platelets , clotting time , bleeding time , were recorded .

On arrival to the operating room, monitors were connected and baseline vital parameters were noted . Two peripheral IV lines with 18 G IV cannula , one for IV infusion and other for the studied drug were started . Preloading was done with 10ml/kg of balanced salt solutions.

Patients received either IV Dexmedetomidine or placebo over a period of 10 min. before induction.

Then anesthesia was induced with inj. Thiopental 5mg/kg , inj. Fentanyl 2mcg/kg and inj. Vecuronium 0.1mg/kg and intubated with appropriate size endotracheal tube .

Anesthesia was maintained with 66% N_2 O, 33% O_2 + IPPV and vecuronium.

The patients' ventilation was controlled to maintain a target value of end tidal co_2 between 33 and 38 mmHg .

One minute pin before pin insertion 1mcg/kg fentanyl and 1.5mg/kg lignocaine were given IV to all patients as a standard in our institute. Then the skull pin, with all its connections were prepared for being attached, was placed within a few minutes. Throughout the operation, 1mcg/kg fentanyl was administered every 45 min until the last 30 min of surgery.

Any incidence of hypotension or bradycardia was recorded. Hypotension is defined as decreased in MAP 30% or more from baseline treated with inj. Ephedrine or Atropine 0.6mg

Hemodynamic measurement and blood sampling

The outcome variables of HR and MAP were recorded at the following time intervals.

- Baseline value 20 min before IV administration of Dexmedetomidine or placebo.
- T_0 : 1 min before the pin insertion.
- T_1, T_5,T_{10}, : 1,5and 10 min , respectively after pin insertion.

Blood samples were obtained 15 min before IV administrations of Dexmedetomidine or placebo (baseline) and at 30 min after the pin

insertion for the determination of plasma glucose, cortisol and prolactin levels.

Results were analyzed and tabulated.

Statistical analysis

Results for parametric data were reported as means± SD

Demographic parameter data were analyzed by student‘t’ tests.

Non parametric data were analyzed using x^2 test

Hemodynamic data and hormone levels were analyzed by the independent‘t’ tests for differences between group and the paired ‘t’ test for differences within groups .

For post- hoc comparison, Bonferroni test was applied .

A value of <0.05 was considered as statistically significant

OBSERVATIONS & ANALYSIS

Table I: Demographic Profile –AGE

Forty patient were taken in to the study group 20 belong to the group NS and remaining 20 belong to DEX .

GROUP		N	Mean	Std. deviation	P
Age in yrs	NORMAL SALINE DEXMED	20 20	41.55 46.10	11.601 11.369	> 0.05 Not significant

The mean age and age distribution in both the groups were found to be similar. P value was found to be not significant

Table 2: Demographic Profile –Sex

			GROUP		TOTAL
			NORMAL SALINE	DEXMED	
SEX	MALE	COUNT % WITHN IN GROUP	12 60.0%	15 75.0%	27 67.5%
	FEMALE	COUNT % WITHN IN GROUP	8 40.0%	5 25.0%	13 32.5%
TOTAL		COUNT % WITHN IN GROUP	20 100.0%	20 100.0%	20 100.0%

Of the 40 patients, 27 were males and 13 were females. The distributions were similar in both the group of patients.

Table 3: Demographic profile -ASA PS status

			GROUP		TOTAL
			NORMAL SALINE	DEXMED	
ASA	I	COUNT % WITHN IN GROUP	6 30.0%	7 35.0%	13 32.5%
	II	COUNT % WITHN IN GROUP	13 65.0%	13 65.0%	26 65.0%
	III	COUNT % WITHN IN GROUP	1 5.0%	0 0%	1 2.5%
TOTAL		COUNT % WITHN IN GROUP	20 100.0%	20 100.0%	40 100.0%

In group NS,6 patients were ASA I, 13 were ASA II , and 1 patient was in ASA III.

In group DEX 7 patients were ASA I, 13 patient were ASA II

The data is statistically not significant ($p>0.05$) and these both groups are comparable in terms of ASA PS status

Table IV : Heart rate changes (beats /min)

	GROUP	N	Mean	Std. Deviation	P
HR - BASELINE	DEX	20	86.05	7.373	P=0.962 not significant
	NS	20	86.15	5.687	
HR - T0	DEX	20	68.00	8.615	<0.05 significant
	NS	20	80.45	5.586	
HR - T1	DEX	20	81.60	7.883	<0.05 significant
	NS	20	99.80	5.578	
HR - T5	DEX	20	75.65	6.968	<0.05 significant
	NS	20	88.70	3.988	
HR - T10	DEX	20	70.70	6.744	<0.05 significant
	NS	20	86.20	3.820	

BASE LINE HEMODYNAMIC PARAMETERS:

There was no statistically significant difference in the base line hemodynamic parameters between the two groups.

The lowest level of heart rate for the DEX group was 68± 8.615 and was observed at T_0. This was significantly lower than the baseline value. Pin attachment significantly increase heart rate at T_1 , $T_5$and T_{10}

Table V : Mean arterial pressure changes (mmHg)

	GROUP	N	Mean	Std. Deviation	P
MAP - BASELINE	DEX	20	97.50	5.267	P=0.849 not
	NS	20	97.80	4.584	significant
MAP - T0	DEX	20	76.95	5.276	<0.05
	NS	20	93.40	5.276	significant
MAP - T1	DEX	20	89.90	4.844	<0.05
	NS	20	119.20	5.053	significant
MAP - T5	DEX	20	86.05	4.989	<0.05
	NS	20	112.55	5.558	significant
MAP - T10	DEX	20	80.45	5.145	<0.05
	NS	20	97.45	4.883	significant

The lowest level of MAP was observed in the DEX group. It was 76.95± 5.276 at T_0. This was significantly lower than the base line value. Pin attachment significantly increased the MAP level at T_1, T_5 and T_{10} (< 0.05)

Table VI: HORMONAL CHANGES – BLOOD SUGAR

GROUP		N	MEAN	Std Deviation	P
RBS-BASELINE	NORMAL SALINE	20	75.15	14.005	=0.317 Not significant
	DEXMED	20	71.30	9.576	
RBS-AFTER	NORMAL SALINE	20	127.90	26.987	< 0.05
	DEXMED	20	05.65	19.535	significant

The base line value was not statistically significant. Sample taken 30 min after pins were statistically significant (P<0.05)

Table VII: HORMONAL CHANGES - PROLACTIN

GROUP		N	MEAN	Std Deviation	P
PROLACTIN – BASELINE	NORMAL SALINE	20	13.6880	9.56236	=0.204 Not significant
	DEXMED	20	10.3490	6.49961	
PROLACTIN -AFTER	NORMAL SALINE	20	60.3050	47.27146	=0.002
	DEXMED	20	22.4325	20.92367	significant

Base line value showed P=0.204 which is not significant while values taken after pin insertion shows P= 0.002 which is statistically significant

Table VIII: HORMONAL CHANGES - CORTISOL

GROUP		N	MEAN	Std Deviation	P
CORTISOL – BASELINE	NORMAL SALINE	20	8.7785	4.55955	=0.416 Not significant
	DEXMED	20	9.9530	4.46692	
CORTISOL – AFTER	NORMAL SALINE	20	20.2505	4.90432	=0.049
	DEXMED	20	16.0930	7.72431	significant

Base line value showed P=0.416 which is not significant while values taken after pin insertion shows a P= 0.049 which is statistically significant

DISCUSSION

This study demonstrated that preoperative administration of single bolus of dexmedetomidine attenuates increase in HR and MAP in neuro surgical patients during skull pin insertion. The concomitant modulation of increases in plasma cortisol , prolactin, and glucose concentrations suggests that this hemodynamic effect is mediated by the sympatholytic properties of dexmedetomidine.

Control of hemodynamic parameters during neurosurgical procedures is of great concern to the neuro-anesthesiologist whose goals include ensuring optimal cerebral perfusion pressure.

Even very deep general anesthesia via inhalation or narcotic, cannot reliably ablate the response to various surgical stimuli and may compromise arterial blood pressure and hence cerebral blood flow in the susceptible patient.

Skull pin insertion is an intense nociceptive stimulus that dramatically increases HR and MAP.

Gonzalez et al[15] studied the hemodynamic response to application of neurological skull pin head holder.

Low et al[16] in their studies of anesthesia in relation to hypertension concluded that the skull pin stimulus is similar to the response to laryngoscopy and intubation, which is mediated by stress hormone release and is exaggerated in patients with chronic hypertension.

Ozkose z,[23] et al believed that it is likely mediated by stress hormones via the same sympathoadrenal reflex .

The insertion of skull pins, though producing similar hemodynamic responses in anesthetized patients, differs from laryngoscopy and intubation in that it is a more reproducible stimulus each time is applied, is less dependent on the skills and timing of the operator, and anatomic considerations. This was thought out by Jellish[17] WS and colleagues.

This "uniform" stimulus should be blunted in neurosurgical patients to avoid unwanted increases in blood pressure, HR and ICP

Costello[18] TG and colleagues had used clonidine to decrease hemodynamic responses to pin head holder application during craniotomy surgeries.

Also, Talke[19] P and colleagues, Bekker A et al, Souter MJ used dexmedetomidine in prevention of hemodynamic and endocrine responses to skull pin placement for craniotomies.

Although lignocaine can be given as local anaesthesia at the sites of the pin insertion , in our institute, both fentanyl and lignocaine were give IV at the same dose and time to all patients. Thus the differences in hemodynamic and neuroendocranial responses between groups could be attributed to dexmedetomidine.

The hemodynamic effects of dexmedetomidine are predictable from the pharmacology of alpha adrenoreceptor agonists[11,24,25].

The hypotensive and bradycardia effects of dexmedetomidine are presumably mediated by the sympatholytic effect of dexmedetomidine. Which is confirmed in this study by significant reduction of cortisol, prolactin and glucose levels in the dexmedetomidine group compared with NS groups.

The most conspicuous neuroendocrine markers of stress are the rapid increase in corticotrophin release hormone, corticotrophin , glucocorticoid (cortisol) levels , the activation of hypothalamic, nor adrenergic output , which enhances glucose production in the liver , and the increased release of the hyper glycaemic hormones adrenaline and glucagon . There is also a fall in insulin levels which is mediated by adrenaline[26].

The prolactin release from the pituitary gland is a very sensitive marker of both physical and psychological stress in mammals. The prolactin surge results from a general increase in the adrenergic activity in the hypothalamus. The stress induced prolactin release is a rapid, strong and transient response that can be evoked by a large number of medical and surgical procedures[26,28]

Therefore in our study investigating the effect of dexmedetomidine in endocrine response to skull pin insertion for craniotomies, we examined both the plasma cortisol and prolactin levels in relation to glucose concentrations.

Dexmedetomidine was not found to affect the process of steriodogenesis, as proven by the work of Venn[29] et al, who demonstrated that dexmedetomidine did not affect the response to adrenocorticotrophic hormone stimulation test. However patients receiving dexmedetomidine in our study had significantly lower intraoperative cortisol levels as compared with those who didn't receive the drug before surgery[30].

Alpha-2 adrenoceptor agonists can cause hyperglycemia in humans[31-34]. The mechanism is thought to involve postsynaptic α-2 adrenoceptor stimulation of pancreatic β-cells, which inhibits insulin

release. We found that dexmedetomidine did inhibit the hyperglycemic response to skull pinning significantly more than placebo, and this may reflect attenuation of sympathoadrenal response. Because of its sympatholytic action, dexmedetomidine suppresses parts of the endocrine surgical stress response with potential impact on perioperative glucose homeostasis[35].Increased plasma concentrations of stress hormones stimulate glucose production, and by counter acting the action of insulin, decreased glucose utilization, resulting in hyperglycemia[8]. In our study 30 min after skull pin insertion plasma cortisol and prolactin level significantly increased in the NS group than the DEX group.

In this study comparison of intravenous dexmedetomidine (1mcg/kg) and placebo was done in attenuating circulatory and neuroendocrine responses to skull pin application.

In patients undergoing general or gynecological surgery, numerous studies have shown that dexmedetomidine blunts cardiovascular response to intubation. In addition to this beneficial property of α_2 agonist, they have also been reported to increase the risk of hypotension and bradycardia. In our study there was no instance of bradycardia, as the bolus drug was given slowly over a period of 10 min.

There could be few limitation of our study. First, we could not measure the plasma catecholamine levels to substantiate our hypothesis owing to the lack of laboratory facilities. The second is that it was performed in patients with good cardiac function. Patients with cardiac disease may be at high risk for developing significant bradycardia and hypotension.

We conclude that preoperative dexmedetomidine administration can be a useful adjuvant in neurosurgical procedures.

SUMMARY

This study was done to compare the efficacy of a bolus injection of dexmedetomidine with a placebo on attenuating the sympathoadrenal response accompanying May Field Skull Pin application in 40 patients divided into two groups

Group DEX: Dexmedetomidine 1mcg/kg

Group NS: Normal saline as a placebo

40 ASA I and II patients aged 18 to 60 yrs undergoing elective craniotomy surgeries under general anesthesia were chosen for the study. After obtaining ethical committee approval the study population was chosen. Informed written consent was obtained from the patients. Heart rate, mean arterial blood pressure, blood sugar values, serum prolactin and cortisol levels were recorded as baseline values.

All patients were monitored with ECG, pulse oximetry, $ETCO_2$ continuously and NIBP intermittently. Patients received study drug just prior to induction of anesthesia according to the group. HR, MAP, was monitored 1 min before insertion of the skull pin and 1, 5and10 min after skull pin insertion. Blood sampling was done for blood sugar, serum

cortisol and serum prolactin levels 20 min before induction of anesthesia and 30 min after skull pin insertion.

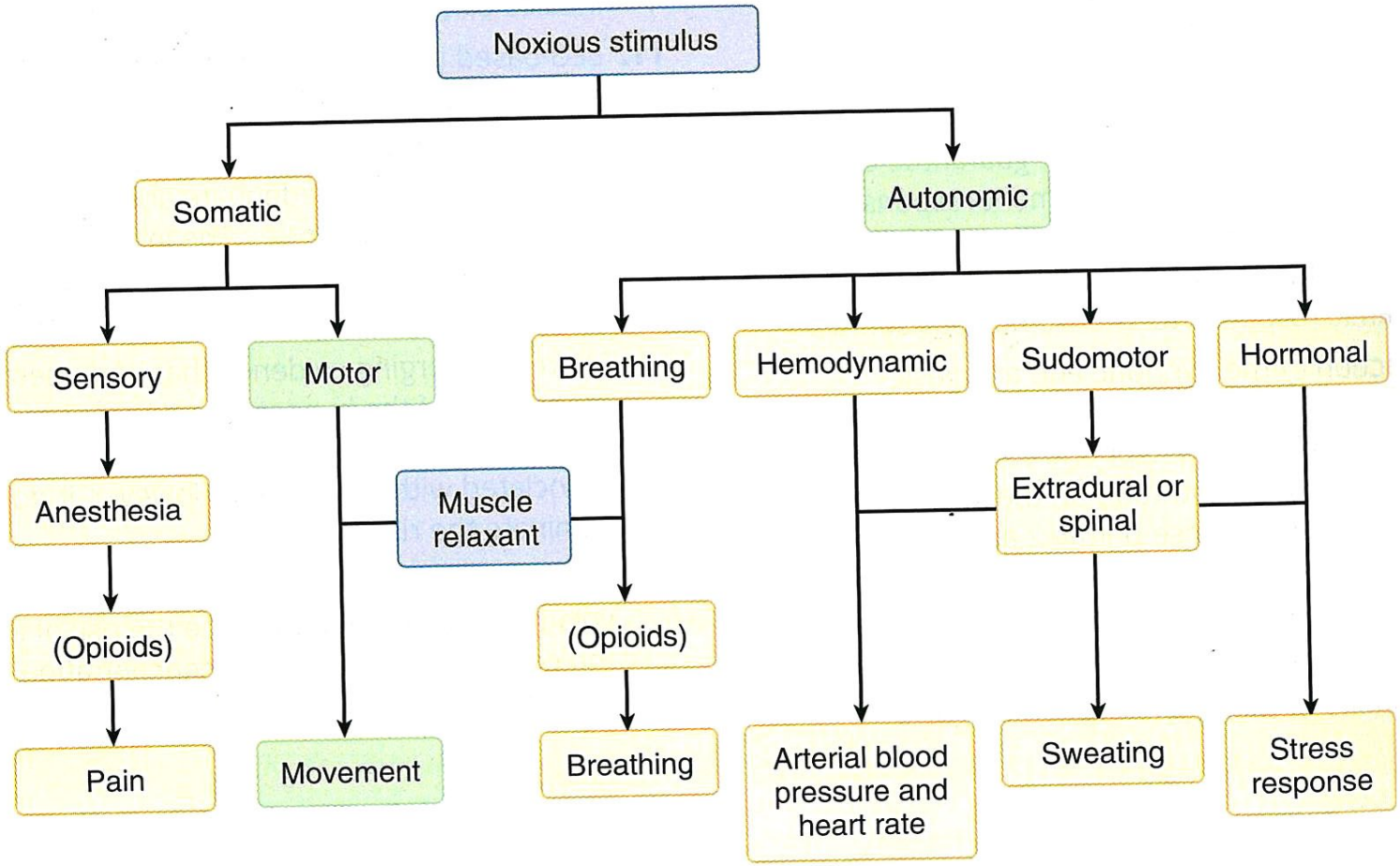
Dexmedetomidine is a highly selective and potent α 2 adrenoreceptor agonist. It is a pure α 2 agonist receptor agonist (α1:α2 ratio – 1:1600) than clonidine which has only less selective agonist activity (α1:α2 ratio 1:200)

In this study which was carried out in the institute of aneasthesiology and critical care at Madras Medical College Hospital, we evaluated the efficacy of dexmedetomidine in attenuating hemodynamic and neuro endocrinal stress response (increase in heart rate and increase in mean arterial pressure) , (increase in blood sugar, serum cortisol, serum prolactin) to May Field Skull Pin insertion .

CONCLUSION

I conclude that dexmedetomidine 1mcg / kg given slowly over 10 min intravenously just prior to induction of anesthesia attenuates the cardiovascular and neuro-endocrinal responses to skull pin head holder application.

May Field Head Rest


Noxious stimulus
Somatic
Autonomic
Sensory
Motor
Breathing
Hemodynamic
Sudomotor
Hormonal
Anesthesia
Muscle relaxant
Extradural or spinal
(Opioids)
(Opioids)
Pain
Movement
Breathing
Arterial blood pressure and heart rate
Sweating
Stress response

NS	Age in Years	Sex	HR - T1	HR- T5	HR - T10	MAP - BL	MAP - T0	MAP - T1	MAP - T5	MAP - T10	RBS -BL	RBS -AFTER	PROLACTIN -baseline	PROLACTIN -AFTER	CORTISOL -	CORTISOL -AFTER
SAKTHIVEL	19	Male	75	71	68	98	78	89	86	81	67	90	16.97	26.02	13.73	19.42
THI RAVIYAM	53	Femal e	70	66	63	96	80	93	90	86	85	177	30.69	128.20	5.66	16.74
THILAGAVATHY	32	Femal e	76	70	66	103	80	92	93	87	56	77	11.12	92.40	3.47	13.46
SHANMUGAM	50	Male	83	77	72	100	81	93	90	80	96	127	40.50	41.76	5.42	7.75
RAMESH	53	Male	90	84	80	88	70	87	84	80	73	99	13.89	23.86	11.46	22.40
KANNAGI	30	Femal e	86	80	76	90	71	80	77	73	68	98	31.62	147.90	5.40	17.89
MUTHU	50	Male	98	92	86	93	70	84	80	74	77	123	10.53	24.62	7.56	23.40
THAYALNAYGI	45	Femal e	86	80	74	100	81	94	90	83	62	103	7.26	160.60	16.98	23.62
GOVINDAMMAL	48	Femal e	73	68	66	97	79	90	87	80	122	135	15.62	58.15	17.49	26.57
SIVA ANANDAN	35	Male	82	77	70	96	78	88	85	80	66	128	8.66	25.54	15.40	27.80
VENKATESHAN	40	Male	96	86	81	109	90	104	95	91	74	120	5.46	10.53	7.64	22.40
PREM KUMAR	36	Male	80	72	71	90	71	86	80	74	66	140	7.53	103.86	3.56	15.46
SARADHA	40	Femal e	86	80	72	92	70	90	92	87	68	132	5.78	23.68	15.76	22.85
RANI	37	Femal e	84	77	73	94	70	86	80	74	78	143	10.56	121.24	7.36	19.47
MANIKANDAN	65	Male	76	70	66	101	76	88	84	80	80	188	10.51	39.36	5.74	24.56
KARRUPAIYAN	53	Male	90	82	76	103	80	92	88	84	77	123	8.54	40.50	6.54	22.56
PUSHPALATHA	26	Femal e	72	68	60	102	81	94	90	84	68	136	5.89	23.66	6.86	17.88
RAMASAMY	29	Male	76	71	65	100	76	89	86	80	70	130	8.56	40.70	7.54	22.36
GOVINDA RAJ	36	Male	75	70	66	97	77	88	80	73	76	156	13.26	54.86	6.12	23.80

MAYAVAN	54	Male	78	72	63	101	80	91	84	78	74	133	10.81	18.66	5.88	14.62

DEXM ED	Age in Years	Sex	ASA	HR -	HR - T0	HR - T1	HR- T5	HR - T10	MAP - BL	MAP - T0	MAP - T1	MAP - T5	MAP - T10	RBS - BL	RBS -	PROLACTIN -	PROLACTIN - AFTER	CORTISOL -BaseLine	CORTISOL -AFTER
VELU	55	Male	II	84	77	101	97	93	102	100	126	120	103	68	88	10.16	16.67	3.22	8.88
DHANABAL	52	Male	II	78	80	96	90	89	96	90	116	113	95	87	112	8.65	24.67	7.03	12.12
KRISHNAVENI	43	Female	I	86	83	98	92	88	98	92	114	110	95	58	72	8.54	18.86	16.62	28.54
POUNAMMAL	50	Female	II	80	79	99	90	87	104	100	118	110	106	70	111	29.61	108.24	14.41	28.76
VELUSAMY	55	Male	I	85	77	90	86	84	100	96	120	109	100	72	101	18.62	19.40	3.77	6.99
BALASUBRAMANI	28	Male	II	92	89	111	90	92	104	100	126	120	104	65	82	5.32	12.30	18.55	21.89
CHELLAMMAL	48	Female	II	97	90	109	91	89	90	82	118	113	88	76	90	7.28	11.62	12.41	18.59
VENUGOPAL	35	Male	I	90	86	100	88	84	96	90	115	108	94	74	92	3.46	28.86	15.22	13.67
PAPPAAMMAL	56	Female	II	82	77	99	89	83	98	98	125	118	99	68	107	18.20	21.42	7.22	19.44
MADAVAN	39	Male	I	87	80	97	90	87	101	96	123	115	98	92	114	12.36	18.30	4.88	7.32
PACHAIAPPAN	42	Male	II	91	78	98	91	87	97	90	110	105	94	72	89	3.88	18.28	6.42	18.31
UDAYAKUMAR	35	Male	I	83	76	100	92	90	96	90	118	103	93	56	123	11.12	20.62	5.74	8.62
GOVINDARAJ	56	Male	II	90	82	104	88	89	104	102	120	118	105	76	140	7.84	18.62	12.72	26.72
SUHASHINI	28	Female	I	79	73	90	80	82	89	88	117	112	92	58	84	4.82	10.50	11.42	13.56
VARADHARAJAN	33	Male	II	85	84	98	86	84	94	90	115	109	94	68	92	5.72	8.72	11.22	18.72
PACHAMUTHU	68	Male	II	86	79	99	90	88	90	92	119	111	96	74	126	7.54	15.34	8.76	12.84
MARIMUTHU	60	Male	II	83	77	93	80	82	96	90	116	109	95	72	117	11.57	23.62	7.03	11.52
SARAVANAN	48	Male	II	93	88	102	86	80	102	100	118	110	104	59	123	18.72	26.32	6.56	1.25
SIVAKOLUNDHU	56	Male	II	77	68	104	86	79	99	90	132	126	96	77	107	5.44	10.77	12.24	18.62

ARUMUGAM	35	Male	I	95	86	108	92	87	100	92	118	112	98	84	143	8.13	15.52	13.62	25.50

NS	Age in Years	Sex	ASA	HR -	HR - T0	HR - T1	HR- T5	HR - T10	MAP - BL	MAP - T0	MAP - T1	MAP - T5	MAP - T10	RBS - BL	RBS -	PROLACTIN – Base Line	PROLACTIN - AFTER	CORTISOL –Base Line	CORTISOL -AFTER
SAKTHIVEL	19	Male	II	89	62	75	71	68	98	78	89	86	81	67	90	16.97	26.02	13.73	19.42
THI RAVIYAM	53	Female	III	73	58	70	66	63	96	80	93	90	86	85	177	30.69	128.20	5.66	16.74
THILAGAVATHY	32	Female	II	83	63	76	70	66	103	80	92	93	87	56	77	11.12	92.40	3.47	13.46
SHANMUGAM	50	Male	II	83	70	83	77	72	100	81	93	90	80	96	127	40.50	41.76	5.42	7.75
RAMESH	53	Male	I	90	77	90	84	80	88	70	87	84	80	73	99	13.89	23.86	11.46	22.40
KANNAGI	30	Female	I	87	73	86	80	76	90	71	80	77	73	68	98	31.62	147.90	5.40	17.89
MUTHU	50	Male	I	102	86	98	92	86	93	70	84	80	74	77	123	10.53	24.62	7.56	23.40
THAYALNAYGI	45	Female	II	85	72	86	80	74	100	81	94	90	83	62	103	7.26	160.60	16.98	23.62
GOVINDAMMAL	48	Female	II	77	55	73	68	66	97	79	90	87	80	122	135	15.62	58.15	17.49	26.57
SIVA ANANDAN	35	Male	II	91	67	82	77	70	96	78	88	85	80	66	128	8.66	25.54	15.40	27.80
VENKATESHAN	40	Male	II	95	83	96	86	81	109	90	104	95	91	74	120	5.46	10.53	7.64	22.40
PREM KUMAR	36	Male	II	80	67	80	72	71	90	71	86	80	74	66	140	7.53	103.86	3.56	15.46
SARADHA	40	Female	II	86	73	86	80	72	92	70	90	92	87	68	132	5.78	23.68	15.76	22.85
RANI	37	Female	I	83	70	84	77	73	94	70	86	80	74	78	143	10.56	121.24	7.36	19.47
MANIKANDAN	65	Male	II	80	63	76	70	66	101	76	88	84	80	80	188	10.51	39.36	5.74	24.56
KARRUPAIYAN	53	Male	II	91	78	90	82	76	103	80	92	88	84	77	123	8.54	40.50	6.54	22.56
PUSHPALATHA	26	Female	I	77	56	72	68	60	102	81	94	90	84	68	136	5.89	23.66	6.86	17.88
RAMASAMY	29	Male	I	99	63	76	71	65	100	76	89	86	80	70	130	8.56	40.70	7.54	22.36
GOVINDA RAJ	36	Male	II	82	60	75	70	66	97	77	88	80	73	76	156	13.26	54.86	6.12	23.80
MAYAVAN	54	Male	II	88	64	78	72	63	101	80	91	84	78	74	133	10.81	18.66	5.88	14.62